REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and the following commentary.

I. Status of Claims

Claim 1 is amended for clarity and to recite "wherein in comparative pharmacokinetic testing with a non-nanoparticulate formulation of meloxicam having the same dosage strength and form, the composition exhibits a smaller T_{max} when compared to a T_{max} of the non-nanoparticulate meloxicam formulation." Support for this comparison is found at paragraph [0014] (non-nanoparticulate meloxicam formulation, e.g. MOBIC® sold by Boehringer Ingelheim Pharmacaeuticals, Inc., of Ridgefield, CT.), Table 4, and the paragraph describing the results in Table 4 at paragraph [0162]. Claims 15 and 17 are amended to delete the repetitive recitation that has been added to claim 1. Accordingly, no new matter has been added.

Claims 13, 42 and 62 are amended to replace the trademarks with the corresponding chemical names. These revisions do not introduce any new matter. Claim 73 has been cancelled without prejudice or disclaimer. Upon entry of this amendment, claims 1-72 will be pending.

II. Double Patenting Rejection

Claims 1-26 and 31-73 were rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-34 of U.S. Patent No. 6,908,626 to Cooper *et al.* in view of U.S. Patent No. 6,221,377 to Meyer *et al.* The amendments to claim 1 obviate the nonstatutory obviousness-type double patenting rejection. Withdrawal of the rejection is respectfully requested.

III. Rejection of Claims under 35 U.S.C. §112

Claims 14-17, 63 and 64 were rejected for alleged lack of written description and lack of enablement. Applicants respectfully traverse the rejections in question.

More specifically, the examiner questioned "how the composition can result in the claimed release profile and the claimed C_{max}" (Office Action, page 4, line 3). As the skilled artisan would have appreciated, C_{max} represents the maximum concentration of a drug in the plasma, and T_{max} stands for the time to reach the maximum concentration. C_{max} and T_{max} are well-known pharmacokinetic features of a drug that one of ordinary skill in the art would identify when studying how the body reacts to the drug in a particular drug form.

The invention is directed to making a stable nanoparticulate meloxicam composition. Due to its smaller size as compared to the conventional meloxicam composition, "the nanoparticulate meloxicam formulations of the invention may exhibit increased bioavailability, and superior C_{max} profiles as compared to conventional prior meloxicam formulations." Specification, paragraph [0025]. Thus, the specification explicitly provides written description that the claimed release profile and C_{max} are achieved by providing a nanoparticulate formation of meloxicam.

By the same token, the specification provides ample support for preparing a stable nanoparticulate formulation of meloxicam. See, for example, paragraphs [0108] – [0114] and Examples 1-3. Therefore, the specification complies with the enablement requirement set forth in 35 U.S.C. §112.

Claims 13, 42, 62 and 73 were rejected for alleged indefiniteness. More specifically, claims 13, 42 and 62 were rejected for improper use of trademarks and claim 73 was rejected for improper multiple dependency.

Claims 13, 42 and 62 have been amended to replace the trademarks with the corresponding chemical names. Claim 73 has been cancelled without prejudice or disclaimer, thereby rendering the rejection moot.

Accordingly, Applicants respectfully request withdrawal of all the rejections under 35 U.S.C. §112.

IV. Rejection of Claims under 35 U.S.C. §103

A. Rejection of claims 1-17, 26-42 and 50-67 over Liversidge and Meyer

Claims 1-17, 26-42 and 50-67 were rejected for allegedly being obvious over WIPO Publication No. WO 93/25190 to Liversidge *et al.* in view of U.S. Patent No. 6,221,377 to Meyer *et al.* Applicants respectfully traverse the rejection.

1. Neither Liversidge Nor Meyer, Alone or in Combination, Teach Each and Every Claimed Feature

Claim 1 as amended requires the meloxicam composition of the invention to have, in comparative pharmacokinetic testing with a non-nanoparticulate formulation of meloxicam of the same dosage strength and form, a smaller T_{max} when compared to a T_{max} of the non-nanoparticulate meloxicam formulation. As acknowledged by the examiner, neither Liversidge nor Meyer alone or in combination fairly teach or suggest any such pharmacokinetic feature, let alone the specifically claimed T_{max}, C_{max}, and release profiles. For at least this reason, the rejection of record has been overcome. Early allowance of the pending claims is respectfully requested.

2. The Rejection Fails to Provide Extrinsic Evidence that Makes Clear that the Claimed T_{max} is Necessarily Present in the Combined References.

Page 6, last paragraph of the Office Action acknowledges that Liversidge does not expressly teach the claimed pharmacokinetic features of the release profile and the C_{max}. The rejection, however, then asserts that the burden has shifted to the applicants to prove that a composition according to the combined references of Liversidge and Meyer would in fact not have the same pharmacokinetics features as claimed. The examiner's support for this assertion is that "Liversidge teaches a nanoparticulate formulation using the claimed surface modifier, carrier, and parameters." With this statement, Applicants infer that the examiner considers such pharmacokinetic features of the claimed meloxicam composition inherent.

MPEP §2163.07(a) and MPEP § 2112IV provide that if the examiner relies upon the theory of inherency, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). MPEP § 2112V provides that only when 1) the referenced product and the claimed invention are proven substantially identical, **and** 2) the examiner has provided evidence or reasoning tending to show the alleged inherent characteristic, *then the burden shifts to the applicant to show an unobvious difference.*

The present rejection lacks any basis in fact and/or technical reasoning to reasonably support the examiner's conclusion that the claimed pharmacokinetic features of T_{max}, release profile, and C_{max} are characteristics that necessarily flow from the teachings of the applied prior art. Accordingly, the burden to show an unobvious difference has not shifted to the applicants. The cited MPEP sections mandate withdrawal of the rejection.

3. A Genus Does not Necessarily Render Obvious the Disclosed Species.

Liversidge relates to an NSAID having a surface modifier adsorbed to the NSAID such that the effective average particle size of the NSAID is less than about 400 nm. The Examiner acknowledges that the primary reference "does not explicitly teach the claimed meloxicam" (Office Action, page 6, first full paragraph), but turns to Meyer for remedy of the deficiency. Nevertheless, Meyer is not in the context of making a nanoparticulate active agent composition but describes enhancing the effect of an analgesic, anti-inflammatory and/or anti-pyretic response-producing effective amount of a medicament with the aid of nitrous oxide in the administration medium. There is only one general statement in the Meyer patent that oxicams include meloxicam, piroxicam and isoxicam.

It appears that the stated rationale in the rejection is that Liversidge discloses a nanoparticulate NSAID composition and meloxicam belongs to the NSAID genus, hence, the prior art renders the claimed nanoparticulate meloxicam species obvious.

This rejection is flawed in several aspects: (i) The secondary reference is not related to a nanoparticulate active agent composition, therefore, the skilled artisan is not motivated to combined the teachings of Liversidge and Meyer; and (ii) The Examiner fails to follows the guidelines set forth in MPEP 2144.08 to establish a *prima facie* obviousness rejection.

(i) The primary reference and the secondary reference are not combinable.

Like the claimed invention, the Liversidge publication relates to a nanoparticulate active agent composition, the method of making the same, and the use of the nanoparticulate active agent composition. In contrast, Meyer discloses an administration medium ingredient that enhances the activity of a medicament. The secondary reference is not in the same context of the primary reference or the invention. For this reason alone, the skilled artisan would not have been motivated to combine these references.

(ii) MPEP 2144.08 sets forth the guidelines for determining obviousness of species when prior art teaches genus, which are not followed by the Examiner.

MPEP 2144.08 clearly prescribes that "the fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness." *In re Baird,* 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) Instead, the Examiner should consider the factors set out in *Graham v. John Deere.* In establishing *prima facie* obviousness, *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966) requires that one must:

(A) determine the scope and contents of the prior art;

(B) ascertain the differences between the prior art and the claims in issue;

(C) determine the level of skill in the pertinent art; and

(D) evaluate any evidence of secondary considerations.

The specification discloses that "not every combination of surface stabilizer and active agent will result in a stable nanoparticulate composition" (paragraph [0033], first sentence). This is further supported by the disclosure of the cited Liversidge reference. Liversidge describes a

screening process to select compatible surface modifiers and NSAIDs (Liversidge, page 10, line 19 *ff*), evidencing that a stable nanoparticulate NSAID is not always obtained. Thus, "it was surprisingly discovered that stable nanoparticulate meloxicam formulations can be made" (specification, paragraph [0033], second sentence).

The claimed nanoparticulate meloxicam composition also achieved unexpected results by exhibiting superior T_{max} and C_{max} profiles. See, for example, paragraphs [0025], [0032] and [0036]. In particular, Table 4 of Example 4 demonstrates that the C_{max} values of lyophilized and liquid dispersion of the nanoparticulate meloxicam composition are increased to 3.42 μg/mL and 3.499 μg/mL, respectively, relative to 2.768 μg/mL of the conventional composition. More significantly, the T_{max} was shortened to 1.292 hours and 0.75 hour, respectively, relative to 3.375 hours for the conventional formulation, which translates into a 2.6-fold and 4.5-fold reduction in T_{max}, respectively. By contrast, Liversidge does not have any suggestion on the profiles of a nanoparticulate meloxicam composition. Instead, it shows that a nanoparticulate naproxen composition reduces the T_{max} by 1.4-fold relative to its conventional counterpart, which is much less than the unexpected results achieved by the claimed nanoparticulate meloxicam composition.

MPEP 2144.08 further guides the Examiner that "when evidence of secondary considerations such as ***unexpected results*** is initially before the Office, for example ***in the specification***, that evidence ***should be considered*** in deciding whether there is a *prima facie* case of obviousness" (emphasis added). There is no evidence on record that the Examiner has considered the unexpected results discussed in the specification. For this reason alone, the Examiner has failed to establish a *prima facie* case of obviousness.

Moreover, MPEP 2144.08 goes on to require the Examiner to "determine whether one of ordinary skill in the relevant art would have been motivated to make the claimed invention as a whole, *i.e.*, to select the claimed species...from the disclosed prior art genus." In fact, this

requirement is essential, because the MPEP prescribes that "some motivation to select the claimed species or subgenus ***must*** be taught by the prior art" (emphasis added).

The Liversidge publication does not explicitly teach meloxicam but only mentions that NSAIDs include oxicams. In fact, in particularly preferred embodiments, the NSAID is naproxen, indomethacin or ibuprofen (page 5, lines 3-4). Accordingly, the prior art does not provide any motivation to select the meloxicam species. The Meyer patent does not compensate for this deficiency, because it merely mentions that meloxicam belongs to the class of drugs called oxicams.

In view of the foregoing discussions, the Examiner has failed to establish a *prima facie* case of obviousness over Liversidge in view of Meyer. Moreover, the unexpectedly obtained stable nanoparticulate meloxicam composition and the unexpected results achieved by the claimed nanoparticulate meloxicam composition are sufficient to rebut any obviousness rejection. Accordingly, Applicants respectfully request withdrawal of the rejection.

B. Rejection of claims 1-17, 26-42 and 50-67 over Ryde and Meyer

Claims 1-17, 26-42 and 50-67 were rejected for allegedly being obvious over U.S. Patent No. 6,375,986 to Ryde *et al.* in view of U.S. Patent No. 6,221,377 to Meyer *et al.* Applicants respectfully traverse the rejection.

The reasons articulated above with respect to the rejection under the combination of Liversidge and Meyer are also applicable to the above-captioned rejection. First, neither Ryde nor Meyer alone or in combination fairly teach or suggest such the amendments to claim 1. Second, the rejection fails to provide extrinsic evidence that makes clear that the claimed T_{max} is necessarily present in the combination of Ryde and Meyer references.

Finally, the teachings of Ryde and Meyer would not lead one of ordinary skill in the art to make their combination. Ryde discloses a solid dose nanoparticulate composition comprising a poorly soluble active agent, at lest one polymeric surface stabilizer and DOSS. Ryde does not

specifically teach a nanoparticulate meloxicam composition and Ryde's composition requires the presence of DOSS. In fact, Ryde further describes that the presence of DOSS is essential because DOSS and the polymeric surface stabilizer exhibit a synergistic effect in redispersion of the solid dose nanoparticulate active agent composition. By contrast, the claimed nanoparticulate meloxicam composition is not limited to a solid dose and does not require DOSS as an ingredient.

Meyer does not remedy the deficiency of the primary reference by its general teaching that oxicams include meloxicam. Also, as discussed above, Meyer is not in the context of making a nanoparticulate active agent composition, so the skilled artisan would not have been motivated to combine the teachings of Ryde and Meyer. Accordingly, Applicants respectfully request withdrawal of the rejection based on Ryde in view of Meyer.

C. Rejection of claims 18-25, 43-49 and 68-73 over Ryde and Meyer

Claims 18-25, 43-49 and 68-73 were rejected for allegedly being obvious over Liversidge *et al.* or Ryde *et al.* in view of WIPO Publication No. WO 01/45706 to Desai *et al.* or U.S. Patent No. 5,384,124 to Courteille *et al.* Without acquiescing to the basis of the rejection, claim 73 has been cancelled without prejudice or disclaimer, thereby rendering the rejection of claim 73 moot. Because claim 1 as argued above is not rendered obvious by the combination of the Ryde and Meyer references, and claims 18-25, 43-49 and 68-72 depend either directly or indirectly from claim 1, they are also not obvious. Withdrawal of the rejection is respectfully requested.

V. Conclusion

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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